I. Remarks

After entry of the amendment, claims 1-2 and 53-55 are pending.

The Related Applications section has been updated.

In order to comply with the restriction requirement, claims 2-52 and 56-81 have been cancelled, without prejudice. Applicants retain the right to pursue the subject matter of these claims in future continuation or divisional applications.

In order to comply with the restriction requirement, claim 54 has been amended to delete the names of the compounds of Formula V and Formulas IX to XVII as these compounds either include a nitroxy lower alkyl ester or do not contain at least one –NO or at least one $–NO_2$ group.

No issues of new mater should arise and entry of the amendment is respectfully requested.

II. Restriction Requirement

The Office Action states that claims 1, 2 and 53-55, wherein X is $-S(O)_o-$ or $-N(R_a)R_i-$; and T is a covalent bond, a carbonyl, $-S(O)_o-$ or $-N(R_a)R_i-$ are withdrawn from consideration pursuant to 37 C.F.R. §1.142 (b) as they are drawn to non-elected inventions and that only claims 1, 2 and 53-55, wherein X is an oxygen and T is an oxygen will be examined.

Applicants respectfully submit that claims 1, 2 and 53-55 are directed to compounds of Formula (I) that must contain at least one –NO group (i.e. nitrosylated) or at least one $–NO_2$ group (i.e. nitrosated). Thus, the prior art for the nitrosated and/or nitrosylated selective cyclooxygenase-2 inhibitor compounds of Formula (I) wherein X is an oxygen and T is an oxygen is the same prior art as the compounds of Formula (I) wherein X is $-S(O)_o-$ or $-N(R_a)R_i-$ and T is a covalent bond, a carbonyl, $-S(O)_o-$ or $-N(R_a)R_i$.. Hence the search and examination of the non-elected species would not place an additional burden on the Examiner as the examiner has already searched all the compounds of Formula I in claim 1 that are nitrosated cyclooxygenase-2 inhibitors (i.e. contain a $-NO_2$ group) or nitrosylated cyclooxygenase-2 inhibitors (i.e. contain a -NO group).

Applicants respectfully request the examination of additional species upon an indication of the allowability of the elected species pursuant to M.P.E P. 803.02. In particular, it is noted that "should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended [to the non-elected species]....The prior art

search will be extended to the extent necessary to determine patentability of the Markush-type claim". M.P.E.P. 803.02.

In view of the above, upon the finding of allowability of the elected species, Applicants respectfully request rejoinder and examination of the additional non-elected species in claim 1 with the pending claims.

III. Claim Objection

Claims 1, 2 and 53-55 are objected to as containing non-elected subject matter.

Claim 54 has been amended to delete the names of the compounds of Formula V and Formulas IX to XVII as these compounds either include a nitroxy lower alkyl ester or do not contain at least one –NO or at least one $-NO_2$ group. As discussed above, the discussion of which is incorporated herein in its entirety, upon the finding of allowability of the elected species, Applicants respectfully request rejoinder and examination of the additional non-elected species in claim 1 with the pending claims.

IV. <u>First Rejection under 35 U.S.C. §103(a)</u>

Claims 1, 2 and 53 are rejected under 35 U.S.C. §103(a) as being unpatentable over Massie et al (U.S. Patent No. 5,844,696).

Applicants respectfully traverse the rejection and respectfully submit that the present claims are unobvious over the cited reference.

Massie et al describes compositions comprising nitrate esters of 2-(2,6-dihalophenylamino) phenylacetoxyacetic acid, the non-steroidal anitinflammatory compound known as diclofenac. Massie does not disclose or suggest nitrate esters of the highly selective cyclooxgenase-2 selective inhibitor of the present invention, known as COX-189 or lumiracoxib. In fact Massie does not even mention COX-189 or lumiracoxib. Thus, Massie is non-analogous art and cannot properly form the basis of an obviousness rejection for the nitrate esters of the selective cyclooxygnease-2 inhibitor of the present invention.

Massie does not disclose or suggest compounds of Formula (I) wherein R_5 is chloro or fluoro; R_9 is chloro, fluoro, triflurormethyl or methyl and R_4 is methyl or ethyl. The compounds of the present invention are not disclosed in Massie, are structurally different from the compounds described in Massie, and have different pharmacological properties from the compounds described in Massie. Additionally there is no motivation for one skilled in the art to

make the claimed nitrosated selective cyclooxygenase-2 inhibitors compounds based on the teachings in Massie.

In support of the difference in the pharmacological properties for the non-steroidal anti-inflammatory compound, diclofenac, disclosed by Massie, and the selective cyclooxygenase-2 inhibitor of Formula (I), COX-189 or lumiracoxib, of the present invention, attached hereto as Appendix 1 is Esser et al., Br, J. Pharmacol., 144: 538-550 (2005). As shown in Table 2, page 544, the inhibitory potencies for the thromboxane B_2 (TxB_2), prostaglandin E_2 (PGE_2) production and COX-2 selectivity for diclofenac and lumiracoxib are different. For the Examiner's convenience Table 2 is shown below:

Table 2 Summary of inhibitory potencies for thromboxane B_2 (TxB_2) and prostaglandin E_2 (PGE_2) production in the human whole blood assay

Treatment (donors)	*TxB_2 (COX-1) IC_{50} (μM)*	*PGE_2 (COX-2) IC_{50} (μM)*	*COX-2 selectivity*
Nonselective COX inhibitors			
Diclofenac (52)	0.097 (±0.001)	0.013 (±0.0001)	7
Ibuprofen (10)	17 (±5)	9 (±0.3)	2
Naproxen (15)	10 (±0.3)	21 (±0.7)	0.5
Selective COX-2 inhibitors			
Celecoxib (14)	7 (±0.3)	0.19 (±0.1)	37
Etodolac (11)	42 (±3)	0.95 (±0.09)	45
Etoricoxib (14)	69 (±5)	0.26 (±0.02)	265
Lumiracoxib (52)	67 (±2)	0.13 (±0.002)	515
Meloxicam (14)	3 (±0.1)	0.11 (±0.004)	26
Nimesulide (7)	35 (±3)	0.69 (±0.05)	51
Rofecoxib (14)	24 (±0.5)	0.17 (±0.01)	141
Valdecoxib (16)	27 (±2)	0.1 (±0.005)	270
Metabolite of lumiracoxib			
4′-hydroxy lumiracoxib (11)	86 (±9)	0.5 (±0.01)	172

Inhibition of TxB_2 and PGE_2 production was determined in separate aliquots of blood that had been pretreated with compounds for 1 h. TxB_2 production was stimulated with the addition of A23187 (50 μM) and assessed after 1 h incubation. PGE_2 production was induced with LPS (10 $\mu g\,ml^{-1}$) and assessed after overnight incubation. Prostanoid production was normalised to percent inhibition and the results from the donors pooled. The IC_{50} indicated here is the mean value for the number of donors indicated in parentheses, along with the s.e.mean. The COX-2 selectivity represents the ratio of IC_{50} for COX-1 divided by COX-2.

The inhibitory potencies for the thromboxane B_2 (TxB_2), prostaglandin E_2 (PGE_2) production and COX-2 selectivity for diclofenac (i.e. the compounds disclosed by Massie) are 0.097 μM, 0.013 μM and 7 respectively. Whereas the inhibitory potencies for the thromboxane B_2 (TxB_2), prostaglandin E_2 (PGE_2) production and COX-2 selectivity for lumiracoxib (i.e. the compounds of the present invention) are 67 μM, 0.13 μM and 515 respectively.

As mentioned above, the selective cyclooxygenase-2 inhibitor compounds of the present invention are structurally different from the non-steroidal anti-inflammatory compounds described in Massie. Additionally there is no motivation for one skilled in the art to make the

claimed nitrosated selective cyclooxygenase-2 inhibitors compounds based on the teachings in Massie.

In view thereof, Applicants respectfully submit that the claims of the present invention are unobvious over the cited reference, and respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

V. Second Rejection under 35 U.S.C. §103(a)

Claims 1 and 2 are rejected under 35 U.S.C. §103(a) as being unpatentable over Del Soldato et al (WO 2001/012584).

Applicants respectfully traverse the rejection and respectfully submit that the present claims are unobvious over the cited reference.

Del Soldato et al describes compositions comprising nitrate esters of 2-(2,6-dihalophenylamino) phenylacetoxyacetic acid, the non-steroidal anitinflammatory compound diclofenac. Del Soldato does not disclose or suggest nitrate esters of the highly selective cyclooxgenase-2 selective inhibitor of the present invention, COX-189 or lumiracoxib. In fact Del Soldato does not even mention COX-189 or lumiracoxib. Thus, Del Soldato is non-analogous art and cannot properly form the basis of an obviousness rejection for the nitrate esters of the selective cyclooxygnease-2 inhibitor of the present invention.

Del Soldato does not disclose or suggest compounds of Formula (I) wherein R_5 is chloro or fluoro; R_9 is chloro, fluoro, triflurormethyl or methyl and R_4 is methyl or ethyl. The compounds of the present invention are not disclosed in Del Soldato and are structurally different from the compounds described in Del Soldato. As mentioned above, the non-steroidal anti-inflammatory compound, diclofenac, disclosed by Del Soldato has different pharmacological properties than the selective cyclooxygenase-2 inhibitor of the present invention. Additionally there is no motivation for one skilled in the art to make the claimed nitrosated selective cyclooxygenase-2 inhibitors compounds based on the teachings in Del Soldato.

In view thereof, Applicants respectfully submit that the claims of the present invention are unobvious over the cited reference, and respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

VI. Third Rejection under 35 U.S.C. §103(a)

Claims 1 and 2 are rejected under 35 U.S.C. §103(a) as being unpatentable over Del Soldato et al (WO 95/30641).

Applicants respectfully traverse the rejection and respectfully submit that the present claims are unobvious over the cited reference.

Del Soldato et al describes compositions comprising nitrate esters of 2-(2,6-dihalophenylamino) phenylacetoxyacetic acid, the non-steroidal anitinflammatory compound diclofenac. Del Soldato does not disclose or suggest nitrate esters of the highly selective cyclooxgenase-2 selective inhibitor of the present invention, COX-189 or lumiracoxib. In fact Del Soldato does not even mention COX-189 or lumiracoxib. Thus, Del Soldato is non-analogous art and cannot properly form the basis of an obviousness rejection for the nitrate esters of the selective cyclooxygnease-2 inhibitor of the present invention.

Del Soldato does not disclose or suggest compounds of Formula (I) wherein R_5 is chloro or fluoro; R_9 is chloro, fluoro, triflurormethyl or methyl and R_4 is methyl or ethyl. The compounds of the present invention are not disclosed in Del Soldato and are structurally different from the compounds described in Del Soldato. As mentioned above, the non-steroidal anti-inflammatory compound, diclofenac, disclosed by Del Soldato has different pharmacological properties than the selective cyclooxygenase-2 inhibitor of the present invention. Additionally there is no motivation for one skilled in the art to make the claimed nitrosated selective cyclooxygenase-2 inhibitors compounds based on the teachings in Del Soldato.

In view thereof, Applicants respectfully submit that the claims of the present invention are unobvious over the cited reference, and respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

VII. Fourth Rejection under 35 U.S.C. §103(a)

Claims 1 and 2 are rejected under 35 U.S.C. §103(a) as being unpatentable over Benedini et al (WO 2000/051988).

Applicants respectfully traverse the rejection and respectfully submit that the present claims are unobvious over the cited reference.

Benedini et al describes compositions comprising nitrate esters of 2-(2,6-dihalophenylamino) phenylacetoxyacetic acid, the non-steroidal anitinflammatory compound diclofenac. Benedini does not disclose or suggest nitrate esters of the highly selective

cyclooxgenase-2 selective inhibitor of the present invention, COX-189 or lumiracoxib. In fact Benedini does not even mention COX-189 or lumiracoxib. Thus, Benedini is non-analogous art and cannot properly form the basis of an obviousness rejection for the nitrate esters of the selective cyclooxygnease-2 inhibitor of the present invention.

Benedini does not disclose or suggest compounds of Formula (I) wherein R_5 is chloro or fluoro; R_9 is chloro, fluoro, triflurormethyl or methyl and R_4 is methyl or ethyl. The compounds of the present invention are not disclosed in Benedini and are structurally different from the compounds described in Benedini. As mentioned above, the non-steroidal anti-inflammatory compound, diclofenac, disclosed by Benedini has different pharmacological properties than the selective cyclooxygenase-2 inhibitor of the present invention. Additionally there is no motivation for one skilled in the art to make the claimed nitrosated selective cyclooxygenase-2 inhibitors compounds based on the teachings in Benedini.

In view thereof, Applicants respectfully submit that the claims of the present invention are unobvious over the cited reference, and respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

VII. <u>Fifth Rejection under 35 U.S.C. §103(a)</u>

Claims 1 and 2 are rejected under 35 U.S.C. §103(a) as being unpatentable over Eek et al (WO 2000/072838).

Applicants respectfully traverse the rejection and respectfully submit that the present claims are unobvious over the cited reference.

Eek et al describes compositions comprising nitrate esters of 2-(2,6-dihalophenylamino) phenylacetoxyacetic acid, the non-steroidal anitinflammatory compound diclofenac. Eek does not disclose or suggest nitrate esters of the highly selective cyclooxgenase-2 selective inhibitor of the present invention, COX-189 or lumiracoxib. In fact Eek does not even mention COX-189 or lumiracoxib. Thus, Eek is non-analogous art and cannot properly form the basis of an obviousness rejection for the nitrate esters of the selective cyclooxygnease-2 inhibitor of the present invention.

Eek does not disclose or suggest compounds of Formula (I) wherein R_5 is chloro or fluoro; R_9 is chloro, fluoro, triflurormethyl or methyl and R_4 is methyl or ethyl. The compounds of the present invention are not disclosed in Eek and are structurally different from the

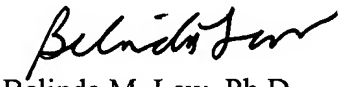
compounds described in Eek. As mentioned above, the non-steroidal anti-inflammatory compound, diclofenac, disclosed by Eek have different pharmacological properties than the selective cyclooxygenase-2 inhibitor of the present invention. Additionally there is no motivation for one skilled in the art to make the claimed nitrosated selective cyclooxygenase-2 inhibitors compounds based on the teachings in Eek.

In view thereof, Applicants respectfully submit that the claims of the present invention are unobvious over the cited reference, and respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.

VIII. Conclusion

An early and favorable reconsideration and allowance of the pending claims is respectfully requested. The Examiner is encouraged to contact the undersigned to expedited prosecution of this application.

Respectfully submitted,



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